(19) Europäisches Patentamt
European Patent Office
Office européen des brevets

(11) Publication number: **0 197 018 B1**

(12) **EUROPEAN PATENT SPECIFICATION**

(45) Date of publication of patent specification: **09.12.92** (51) Int. Cl.5: **C07J 3/00**

(21) Application number: **86850103.2**

(22) Date of filing: **21.03.86**

Divisional application 89116726.4 filed on 21/03/86.

The file contains technical information submitted after the application was filed and not included in this specification

(54) **16,17-Acetal-substituted androstane-17-beta-carboxylic-acid esters, process for their preparation and pharmaceutical compound containing them.**

(30) Priority: **04.04.85 SE 8501693**

(43) Date of publication of application:
08.10.86 Bulletin 86/41

(45) Publication of the grant of the patent:
09.12.92 Bulletin 92/50

(84) Designated Contracting States:
AT BE CH DE FR GB IT LI LU NL SE

(56) References cited:
EP-A- 0 143 764
DE-A- 3 126 732
DE-A- 3 149 475
SE-A- 378 109
SE-A- 396 079
SE-A- 436 572
US-A- 3 828 080
US-A- 3 981 894

(73) Proprietor: **Aktiebolaget Draco**
Box 34
S-221 00 Lund(SE)

(72) Inventor: **Andersson, Paul Hakan**
Gullvingevägen 12
S-240 17 Södra Sandby(SE)

Inventor: **Andersson, Per Ture**
Fagelhundsvägen 8
S-222 53 Lund(SE)
Inventor: **Axelsson, Bengt Ingemar**
Lillegardsvägen 5
S-240 13 Genarp(SE)
Inventor: **Thalen, Bror Arne**
Morkullevägen 35
S-237 00 Bjärred(SE)
Inventor: **Trofast, Jan William**
Vapenkroken 34
S-222 47 Lund(SE)

(74) Representative: **Danielsson, Sten Ove et al**
AB ASTRA Patent and Trademark Department
S-151 85 Södertälje(SE)

Rank Xerox (UK) Business Services

Description

Field of the Invention

The present invention relates to novel, pharmacologically active compounds and to intermediates and a process for their preparation. The invention also relates to pharmaceutical compositions containing the compounds useful for the treatment of inflammatory, allergic, muscoskeletal or dermatological conditions.

The object of the invention is to provide a glucocorticosteroid which possesses high anti-inflammatory potency on the place of application and low glucocorticoid systemic potency.

Background Art

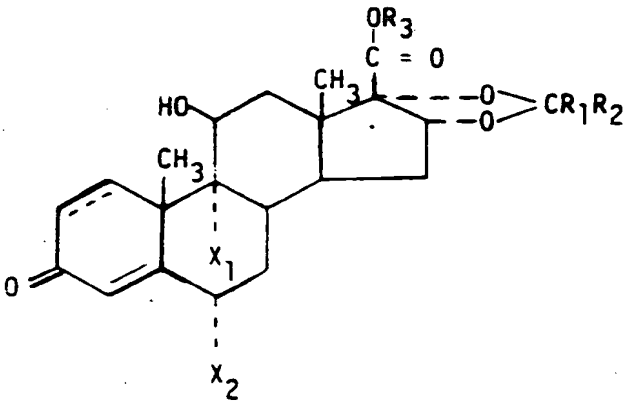
It is known that certain glucocorticosteroids (GCS) can be used for local therapy of inflammatory, allergic or immunologic diseases in respiratory airways (e.g. asthma, rhinitis), in skin (eczema, psoriasis) or in bowel (ulcerative colitis, Morbus Crohn). With such local glucocorticoid therapy, clinical advantages over general therapy (with e.g. glucocorticoid tablets) are obtained, especially regarding reduction of the unwanted glucocorticoid effects outside the diseased area. To reach such clinical advantages, in e.g. severe respiratory airway disease, GCS must have a suitable pharmacological profile. They should have high intrinsic glucocorticoid activity at the application site but also a rapid inactivation by e.g. hydrolysis in the target organ or after uptake into the general circulation.

Since binding of GCS to the glucocorticoid receptor is a pre-requisite for their anti-inflammatory and allergic effects to occur, the ability of steroids to bind to their receptor(s) can be used as an adequate method for determining the biological activity of GCS. A direct correlation between the affinity of GCSs to the receptor and their antiinflammatory effects has been shown using ear edema test in the rat. [Correlation between chemical structure, receptor binding, and biological activity of some novel, highly active. 16α,17α-acetalsubstituted glucocorticoids. E. Dahlberg, A. Thalén, R. Brattsand, J-Å Gustafsson, U. Johansson, K. Roempke, and T. Saartok, Mol. Pharmacol. 25 (1984), 70.]

Disclosure of the Invention

The present invention is based on the observation that certain 3-oxo-androsta-1,4-diene-17α-carboxylic acid esters possess high binding affinity to the glucocorticosteroid receptor. The compounds of the invention can be used for the treatment and control of inflammatory conditions.

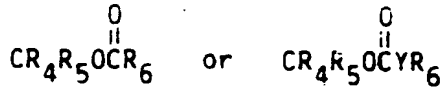
The compounds of the invention are characterized by the formula wherein



I

the 1,2-position is saturated or is a double bond

- X_1 is selected from hydrogen, fluorine, chlorine and bromine
- X_2 is selected form hydrogen, fluorine, chlorine and bromine
- R_1 is selected from hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon atoms
- R_2 is selected from hydrogen or straight and branched hydrocarbon chains having 1-10 carbon atoms and
- R_3 is selected from



Y is O or S

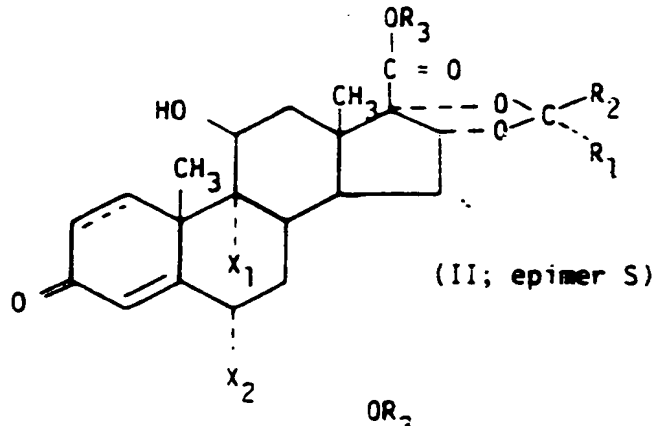
R_4 is selected from hydrogen, straight or branched hydrocarbon chains having 1-10 carbon atoms or from phenyl

R_5 is selected from hydrogen or methyl and

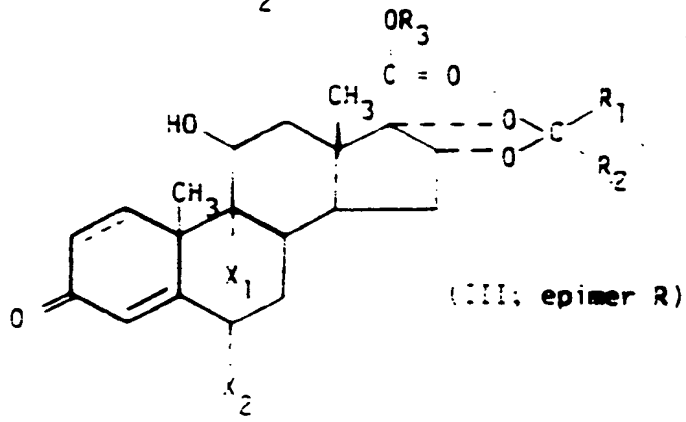
R_6 is selected from hydrogen, straight or branched, saturated or unsaturated hydrocarbon chains having 1-10 carbon atoms, an alkyl group substituted by at least one halogen atom, a heterocyclic ring system containing 3-10 atoms in the ring system, $-(CH_2)_m\ CH(CH_2)_n$ (m = 0,1,2; n = 2,3,4,5,6), phenyl or benzyl groups which are unsubstituted or substituted by one or more alkyl, nitro, carboxy, alkoxy, halogen, cyano, carbalkoxy or trifluoromethyl group(s),

provided that R_1 and R_2 are not simultaneously hydrogen.

The individual stereoisomeric components present in a mixture of a steroid having the above formula (I) can be elucidated in the following way:

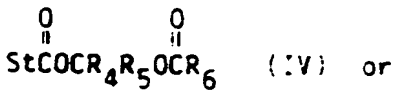


(II; epimer S)

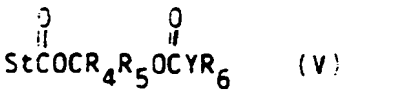


(III; epimer R)

The individual stereoisomeric components present, in a mixture of steroid 17β-carboxylic acid esters having the formulas

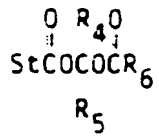


(IV) or

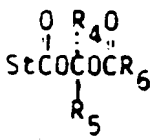


(V)

where St is the steroid moiety, can be elucidated in the following way

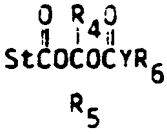


VI

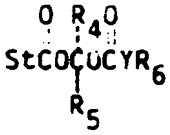


VII

and



VIII



IX

In diasteroisomers like II, III, VI, VII, VIII and IX, the configuration differs only at one out of several asymmetric carbon atoms. Such diastereoisomers are denoted epimers.

Alkyl in the definitions above is a straight or branched hydrocarbon chain with 1-5 carbon atoms, preferably 1-4 C.

Alkoxy in the definition above is a group -O-alkyl wherein the alkyl moiety has the above given definition.

Halogen in the definition above is preferably a chlorine, bromine or fluorine atom.

Carbalkoxy in the definition above is a group -COO-alkyl wherein the alkyl moiety has the above given definition.

Heterocyclic ring system is a ring system containing as hetero atoms N, O or S.

Preferred systems are pyrrolyl, pyridyl, pyrimidyl, pyrazinyl, furyl, pyranyl, benzofuranyl, indolyl and thienyl.

Particular compounds of the invention which are preferred:

1'-Ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate, the epimeric mixture A + B and epimer B.

1'-isopropoxycarbonyloxyethyl 9α-fluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate, epimer B.

1'-propoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]androxta-1,4-diene-3-one-17β-carboxylate, epimer B.

1'-isopropoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate, epimeric mixture A + B and epimer B.

1'-Acetoxyethyl (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate, epimer B.

1'-Ethoxycarbonyloxyethyl (22R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate, epimer B.

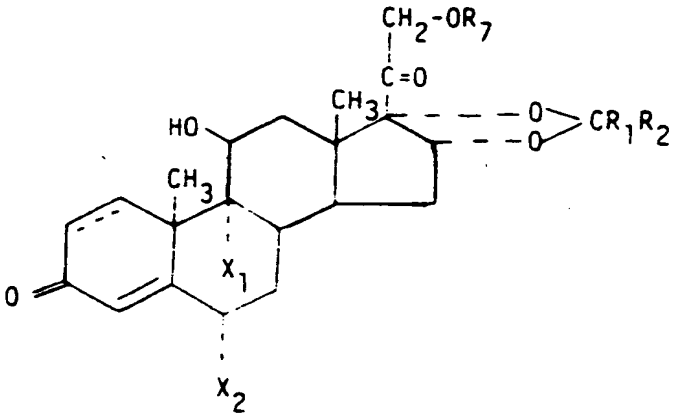
1'-isopropoxycarbonyloxyethyl (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-

diene-3-one-17β-carboxylate, epimer B.

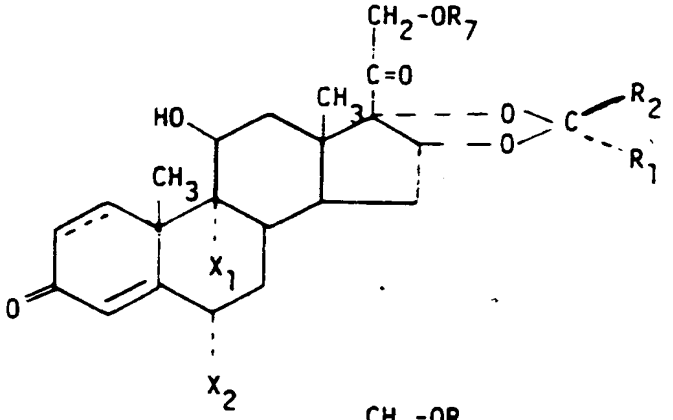
1'-Ethoxycarbonyloxyethyl (20R)-6α,9α-difluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate, epimeric mixture A + B and epimer B.

Methods of Preparation

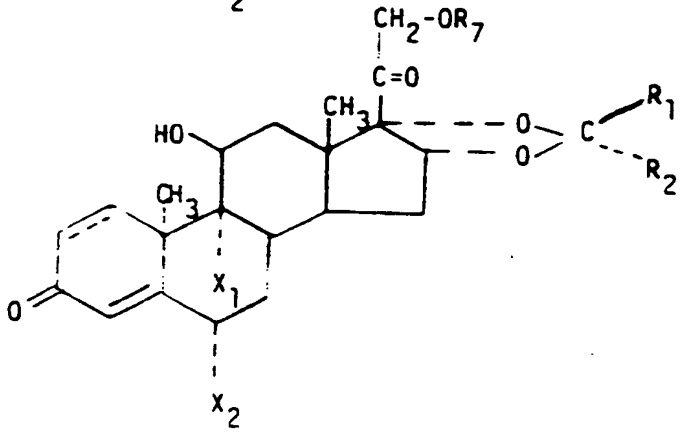
The compounds of the invention are prepared by the oxidation of a compound of the formulas X, XI and XII to the corresponding 17β-carboxylic acid:



X



XI



XII

wherein

the solid and broken lines between C-1 and C-2 represent a single or double bond,

X_1, X_2, R_1 and R_2 have the meaning given above, and R_7 is hydrogen or an acyl group with 1-10 carbon

atoms arranged in a straight or branched chain.

The 17β-carboxylic acids then are esterified to give compounds characterized by the formula I-IX, wherein --- X_1, X_2, R_1, R_2 and R_3 have the meaning given above.

The process of this invention to convert a compound of formulas X, XI or XII to the corresponding 17-carboxylic acids is carried out in a suitable oxygenated hydrocarbon solvent such as a lower alkanol. Methanol and ethanol are preferred, particularly the former. The reaction medium is made slightly alkaline by the addition of a suitable weak inorganic base such as an alkali metal carbonate, for example sodium, lithium or potassium carbonate. The latter is preferred. The conversion of a compound of formula X, XI or XII to a 17β-carboxylic acid of formula I, II or III (R_3 = H) takes place at ambient temperatures, i.e. 20-25 °C.

The presence of oxygen is necessary for the reaction. Oxygen can be supplied by bubbling a stream of air or oxygen into the reaction mixture.

The oxidative degradation of the 17β side-chain of compounds of formula X, XI and XII to the corresponding 17β carboxylic acids can also be carried out with periodic acid, sodium hypobromate or with sodium bismuthate. The reaction is performed in a mixture of water and a suitable oxygenated hydrocarbon solvent such as a lower ether. Dioxane and tetrahydrofurane are preferred, particularly the former.

The parent 17β-carboxylic acids of compounds of formula I, II and III (R_3 = H) may be esterified in known manner to provide 17β carboxylate esters according to the invention. For example, the 17β-carboxylic acid may be reacted with an appropriate alcohol and a carbodiimide, e.g. dicyclohexylcarbodiimide, in a suitable solvent such as diethylether, tetrahydrofurane, methylene chloride or pyridine advantageously at a temperature of 25-100 °C. Alternatively, a salt of the 17β-carboxylic acid with an alkali metal, e.g. lithium, sodium or potassium, a salt of a quaternary ammonium compound, such as a salt of triethyl-or tributylamine, or tetrabutylammonium, may be reacted with an appropriate alkylating agent, for example an acyloxyalkylhalide or haloalkyl alkylcarbonate preferably in a polar solvent medium such as acetone, methylethylketone or dimethyl formamide, dimethyl sulphoxide, methylenechloride or chloroform, conveniently at a temperature in the range 25-100 °C. The reaction may also be performed in the presence of a crown ether.

The crude steroid ester derivatives formed are after isolation purified by chromatography on a suitable material, for instance cross-linked dextran gels of Sephadex® LH-type with suitable solvents as eluants, e.g. halogenated hydrocarbons, ethers, esters such as ethyl acetate or acetonitrile.

The individual epimers, which are formed at the acetalisation of the 16α,17α-hydroxy groups or at the esterification of the 17β-carboxylic acids, possess practically identical solubility characteristics. Accordingly, they have turned out to be impossible to separate and isolate from the epimeric mixture by conventional method for resolution of stereoisomers. e.g. fractionated crystallization. In order to obtain the individual epimers separately the stereoisomeric mixtures according to the formulas I, IV and V above are subjected to column chromatography. thus separating the epimes II, III, VI, VII, VIII and IX in view of different mobility on the stationary phase. The chromatography may be carried out for instance on cross-linked dextran gels of the type Sepnadex® LH. e.g. Sephadex® LH-20 in combination with a suitable organic solvent as eluting agent. Sephadex® LH-20, prepared by Pharmacia Fine Chemicals AB. Uppsala, Sweden, is a beadformed hydroxypropylated dextran gel wherein the dextran chains are cross-linked to give a three-dimensional polysaccharide network. As eluting agent, halogenated hydrocarbons, e.g. chloroform or a mixture of heptane-chloroform-ethanol in the proportions 0-50:50-100:10-1 has successfully been used, preferably a 20:20:1 mixture.

Pharmaceutical Preparations

The compounds of the invention may be used for different modes of local administration dependent on the site of inflammation, e.g. percutaneously, parenterally or for local administration in the respiratory tract by inhalation. An important aim of the formulation design is to reach optimal bioavailability of the active steroid ingredient. For percutaneous formulations this is advantageously achieved if the steroid is dissolved with a high thermodynamic activity in the vehicle. This is attained by using a suitable system of solvents comprising suitable glycols, such as propylene glycol or 1,3-butandiol either as such or in combination with water.

It is also possible to dissolve the steroid either completely or partially in a lipophilic phase with the aid of a surfactant as a solubilizer. The percutaneous compositions can be an ointment, an oil in water cream, a water in oil cream or a lotion. In the emulsion vehicles the system comprising the dissolved active component can make up the disperse phase as well as the continuous one. The steroid can also exist in the above compositions as a micronized, solid substance.

Pressurized aerosols for steroids are intended for oral or nasal inhalation. The aerosol system is

designed in such a way that each delivered dose contains 10-1000 µg, preferably 20-250 µg of the active steroid. The most active steroids are administered in the lower part of the dose range. The micronized steroid consists of particles substantially smaller than 5 µm, which are suspended in a propellent mixture with the assistance of a dispersant, such as sorbitan trioleate, oleic acid, lecithin or sodium salt of dioctylsulphosuccinic acid.

Working Examples

The invention will be further illustrated by the following non-limitative examples. In the examples a flow-rate of 2.5 ml/cm^2 • h^{-1} is used at the preparative chromatographic runs. Molecular weights are in all examples determined with electron impact mass spectrometry and the melting points on a Leitz Wetzlar hot stage microscope. All HPLC analyses (HPLC = High Performance Liquid Chromatography) were performed on a Waters µßondapak C_{18} column (300x3.9 mm internal diameter) with a flow-rate of 1.0 ml/min and with ethanol-water in ratios between 50:50 and 60:40 as mobile phase, if not otherwise stated.

Example 1. This example sets forth a process for preparing 11β-hydroxy-16α,17α-[(1-methylethylidene)bis-(oxy)] - and (20RS)-, (20R)- and (20S)-11β-hydroxy-16α,17α-alkylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylic and -4-ene-3-one-17β-carboxylic acids.

Preparation of 6α,9α-difluoro-11β-hydroxy-16α,17α[(1-methylethylidene)-bis(oxy)]androsta-1,4-diene-3-one-17β-carboxylic acid.

A. To a solution of 1.99 g of fluocinolone 16α,17α-acetonide in 120 ml of methanol 40 ml of 20% aqueous potassium carbonate was added. A stream of air was bubbled through this solution for about 20 h under stirring at room temperature. The methanol was evaporated and 200 ml of water was added to the residue. The solution was extracted with methylene chloride. The aqueous phase was acidified with diluted hydrochloric acid. The precipitate formed was collected by filtration and dried to yield 1.34 g of 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)-bis(oxy)]androsta-1,4-diene-3-one-17β-carboxylic acid, melting point 264-68 °C, molecular weight 438. The purity determined by HPLC was 94.0%. The aqueous phase was extracted with ethyl acetate. After drying the solvent was evaporated leaving another 0.26 g portion of acid. Purity: 93.7%.

B. Periodic acid (15.1 g) in 16.5 ml of water was added to a solution of fluocinolone 16α,17α-acetonide (5.0 g) in 55 ml dioxane. The reaction mixture was stirred at room temperature for 20 h, neutralized with saturated aqueous sodium hydrogen carbonate and evaporated. The residue was dissolved in 200 ml of methylene chloride and washed with 8 x 100 ml 10% aqueous potassium carbonate. The aqueous phase was acidified with conc. hydrochloric acid and extracted with 6 x 100 ml of ethyl acetate. After drying the solvent was evaporated. The residue was dissolved in 400 ml of ethyl acetate and precipitated with petroleum ether yielding 3.96 g of 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis-(oxy)]-androsta-1,4-diene-3-one-17β-carboxylic acid. The purity determined by HPLC was 99.5%

C. Similarly, by following the procedure set forth in the example by substituting fluocinolone 16α,17α-acetonide for 11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione, 6α-fluoro-11β,16α,17α,21-tetrahydroxypregna-1,4-diene-3,20-dione, and triamcinolone 16α,17α-acetonide 11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]androsta-1,4-diene-3-one-17β-carboxylic acids are prepared. By substituting the 16α,17α-acetonide group for 16α,17α-acetals between 16α-hydroxyprednisolone 6α-fluor-16α-hydroxyprednisolone, triamcinolone and fluocinolone and acetaldehyde, propanal, butanal, isobutanal, pentanal, 3-methylbutanal, 2,2-dimethylpropanal, hexanal, heptanal, octanal, nonanal and dodecanal and their 21-esters (20RS)- (20R)- and (20S)-11β-hydroxy-16α,17α-alkylmethylenedioxyandrosta-1,4-diene- and 4-ene-3-one-17β-carboxylic acids are prepared.

Example 2 1'-Ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16a,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate.

A. 6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylic acid (600 mg) and potassium hydrogen carbonate (684 mg) were dissolved in 45 ml of dimethyl formamide. 1-Bromoethyl ethyl carbonate (2 ml) was added and the reaction mixture stirred at room temperature overnight. Water (200 ml) was added and the mixture was extracted with methylene chloride. The combined extracts were washed with 5% aqueous sodium hydrogen carbonate and water, and the residue purified by chromatography on a Sephadex LH-20 column (72x6.3 cm) using chloroform

as mobil phase. The fraction 1515-2250 ml was collected and evaporated yielding 480 mg of 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate. The purity determined by HPLC was 96.1% and the ratio epimer A/B, 48/52. Melting point: 218-27 °C. $[\alpha]_D^{25}$ = +63.2° (c = 0.214; CH_2Cl_2). The molecular weight was 554.

The 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate (480 mg) was chromatographed on a Sephadex LH-20 column (76x6.3 cm) using heptane:chloroform:ethanol. 20:20:1, as mobile phase. The fraction 2325-2715 ml was collected, evaporated and the residue dissolved in methylene chloride and precipitated by petroleum ether giving 200 mg of a compound (A) of purity 97.3% (determined by HPLC analysis). Melting point: 246-50 °C. $[\alpha]_D^{25}$ = +100.5° (c = 0.214; CH_2Cl_2). The molecular weight was 554.

The fraction 4140-5100 ml yielded 250 mg of a compound (B) with purity 99.0%. Melting point: 250-55 °C. $[\alpha]_D^{25}$ = +28.5° (c = 0.246; CH_2Cl_2). The molecular weight was 554. The methine signal from the ester group is shifted 0.13 ppm downfield in ^{1}H-NMR spectrum of B compared to A, while the rest of the spectra are nearly identical. The electron impact mass spectra of A and B are identical apart from the intensities of the mass peaks. These spectroscopic differences and similarities indicate that A and B are epimers due to the chiral centre in the ester group.

B. 6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylic acid (200 mg) was dissolved in 25 ml of dimethylformamide. 1-Chloroethyl ethyl carbonate (100 mg), potassium hydrogen carbonate (70 mg) and 18-crown-6-ether were added. The reaction mixture was stirred at 80 °C for 3 h, cooled, extracted with methylene chloride after addition of 150 ml of water, dried and evaporated. The crude product was purified in the same way as in procedure A leaving 207 mg of 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylate. The purity (HPLC) was 98.4% and the ratio epimer A/B, 54/46.

C. 6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylic acid (200 mg) and 1,5-diazabicyclo [5.4.0] undecene-5 (140 mg) were suspended in 25 ml of benzene and warmed to reflux. A solution of 1-bromoethyl ethyl carbonate (175 mg) in 5 ml of benzene was added and the mixture was refluxed for 2 1/2 h. After cooling 50 ml of methylene chloride was added and the solution was washed with water, dried and evaporated. The crude product was purified in the same way as in procedure A, yielding 207 mg of 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylate. The purity (HPLC) was 96.4% and the ratio epimer A/B, 44/56.

D. To a solution of 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethyl-idene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylic acid (100 mg) in 25 ml of acetone 175 mg of α-bromodiethylcarbonate and 45 mg of anhydrous potassium carbonate were added. The mixture was heated for 6 h at reflux. The cooled reaction mixture was poured into 150 ml of water and extracted with methylene chloride. The extract was washed with water, dried over sodium sulphate and evaporated yielding 65 mg of solid 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α, [(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylate. The purity determined by HPLC was 97.6% and the ratio epimer A/B, 49/51.

E. 6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylic acid (500 mg) and tetrabutylammonium hydrogen sulphate (577 mg) were added to 3 ml of 1M sodium hydroxide.A solution of 435 mg of 1-bromoethyl ethyl carbonate in 50 ml of methylene chloride was added. The mixture was refluxed with stirring overnight. The two layers were separated. The organic layer as washed with 2x10 ml of water, dried and evaporated. The crude product was purified by chromatography on a Sephadex LH-20 column (72x6.3 cm) using chloroform as mobile phase. The fraction 1545-1950 ml was collected and evaporated and the residue precipitated from methylene chloride - petroleum ether leaving 341 mg of 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)-bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylate. The purity determined with HPLC was 99.2% and the ratio epimer A/B, 56/44.

F. 6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis-(oxy)] androsta-1,4-diene-3-one-17β-carboxylic acid (200 mg) and tricaprylmethylammonium chloride (200 mg) were added to 5 ml of saturated aqueous $NaHCO_3$. A solution of 100 mg of 1-bromoethyl ethyl carbonate in 10 ml of methylene chloride was added. The mixture was stirred at 45 °C for 20 h, diluted with 10 ml of methylene chloride and isolated and purified in the same way as in procedure E yielding 254 mg of 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] - androsta-1,4-diene-3-one-17β-carboxylate. The purity (HPLC) was 97.4% and the ratio epimer A/B, 60/40.

G. 6α,9α--Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-car-

boxylic acid (200 mg), 1-bromoethyl ethyl carbonate (135 mg) and triethylamine (275 mg) were dissolved in 20 ml of dimethylformamide. The mixture was stirred at 80 °C for 3 h, diluted with 200 ml of methylene chloride, washed with water, dried and evaporated. The crude product was purified in the same way as in procedure A yielding 69 mg of 1'-ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylate. The purity (HPLC) was 97.8% and the ratio epimer A/B, 48/52.

Example 3 1'-Acetoxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylate.

6α,9α-Difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)] androsta-1,4-diene-3-one-17β-carboxylic acid (500 mg) and potassium hydrogen carbonate (575 mg) were dissolved in 40 ml of dimethylformamide. 1-chloroethyl acetate (1 ml) was added and the reaction mixture was stirred at room temperature for 40 h. The reaction mixture was poured into 50 ml of water and extracted with methylene chloride. The extract was washed with aqueous sodium hydrogen carbonate and water, dried and evaporated. The residue was chromatographed on Sephadex LH-20 column (72x6.3 cm) using chloroform as mobile phase. The fractions 1755-2025 and 2026-2325 ml were collected and evaporated.

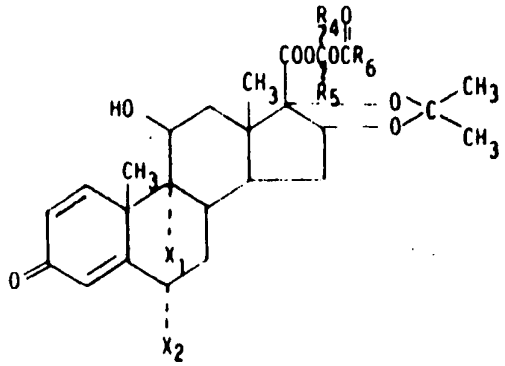
The solid product from fraction 1755-2025 ml was further purified by chromatography on a sephadex LH-20 column (76x6.3 cm i.d.) using a mixture of heptane-chloroform-ethanol, 20:20:1, as mobile phase. The fraction 2505-2880 ml was collected and evaporated. the residue was dissolved in methylene chloride and precipitated with petroleum ether leaving 167 mg of solid product (A). The purity determind by HPLC was 99.1%. Melting point 238-59 °C. $[\alpha]_D^{25}$ = +94° (c = 0.192; CH_2Cl_2). The molecular weight was 524.

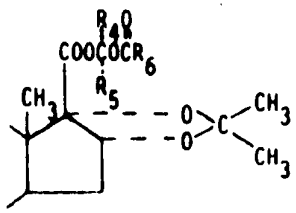
The solid product from fraction 2026-2325 ml above was further purified by chromatography in the same way as above. The fraction 5100-5670 ml was collected and evaporated. The residue was dissolved in methylene chloride and precipitated with petroleum ether yielding 165 mg of solid product (B). The purity determined with HPLC was 99.4%. Melting point 261-65 °C. $[\alpha]_D^{25}$ = +34° (c = 0.262; (CH_2Cl_2). The molecular weight was 524.

The ^{1}H-NMR spectra of A and B are nearly identical with the exception of the methine quartet from the ester group which is shifted 0.16 ppm downfield in compound B compared to A. The fragmentation patterns of A and B in electron impact mass spectra are identical apart from the intensities of the mass peaks. These spectroscopic properties of A and B indicate that they are epimers due to the chiral centre in the ester group.

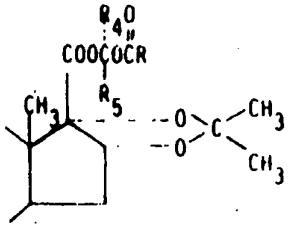
Example 4-86 The substance given in Table 1-3 below were prepared, isolated and purified in a manner analogous to that described in Examples 2 and 3.

Table 1.





Epimer A



Epimer B

Example no.	X_1	X_2	R_4	R_5	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	Molecular weight found	Retention volume (ml)
4	H	H	fenyl	H	CH_3	A	242 (dec)	+79°	550.7	550	1665-1890[1)]
5	H	H	fenyl	H	CH_3	B	221 (dec)	+89°	550.7	550	1891-2175[1)]
6	F	H	$CH(CH_3)_2$	H	CH_3	A	-	+102°	534.6	534	2325-2580[1)]
7	F	H	$CH(CH_3)_2$	H	CH_3	B	-	+40°	534.6	534	3165-3555[1)]
8	F	H	fenyl	H	CH_3	A	249 (dec)	+73°	568.6	568	2040-2355[1)]
9	F	H	fenyl	H	CH_3	B	238 (dec)	+75°	568.6	568	2895-3285[1)]
10	F	F	CH_3	H	$C(CH_3)_3$	A	262-70	+87°	566.6	566	2190-2505[1)]
11	F	F	CH_3	H	$C(CH_3)_3$	B	268-77	+50°	566.6	566	3525-3990[1)]

Table 1. (continued)

Example no.	X_1	X_2	R_4	R_5	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	Molecular weight found	Retention volume (ml)
12	F	F	CH_3	H	fenyl	A	224-30	+96°	586.6	586	2325-2625 [1]
13	F	F	CH_3	H	fenyl	B	259-67	+48°	586.6	586	4350-4875 [1]
14	F	F	CH_3	CH_3	CH_3	-	130-42	+61°	538.6	538	1965-2220 [1]
15	F	H	CH_3	H	$OC(CH_3)_3$	A	184-87	+98°	564.7	564	235-280 [3]
16	F	H	CH_3	H	$OC(CH_3)_3$	B	>300	+30°	564.7	564	525-630 [2]
17	H	F	CH_3	H	$OCH(CH_3)_2$	A	250-53	+109°	550.6	550	1530-1770 [1]
18	H	F	CH_3	H	$OCH(CH_3)_2$	B	230-35	+58°	550.6	550	2295-2850 [1]
19	F	F	CH_3	H	OCH_3	A	235-42	+102°	540.6	540	590-690 [2]
20	F	F	CH_3	H	OCH_3	B	225-33	+31°	540.6	540	395-430 [3]
21	F	F	CH_3	H	$O(CH_2)_2CH_3$	A	224-31	+106°	568.6	568	410-495 [2]
22	F	F	CH_3	H	$O(CH_2)_2CH_3$	B	227-30	+28°	568.6	568	690-900 [2]
23	F	F	CH_3	H	$OCH(CH_3)_2$	A+B	205-28	+59°	568.6	568	1365-1560 [5]
24	F	F	CH_3	H	$OCH(CH_3)_2$	A	210-25	+95°	568.6	568	400-475 [2]
25	F	F	CH_3	H	$OCH(CH_3)_2$	B	242-47	+31°	568.6	568	625-780 [2]
26	F	F	CH_3	H	$OCH(CH_2CH_3)_2$	A	226-28	+95°	596.7	596	1785-2085 [1]
27	F	F	CH_3	H	$OCH(CH_2CH_3)_2$	B	183-97	+30°	596.7	596	3150-3600 [1]
28	F	F	CH_3	H	$OCH_2CH(CH_2CH_3)_2$	A	217-21	+89°	610.7	610	1725-1980 [1]
29	F	F	CH_3	H	$OCH_2CH(CH_2CH_3)_2$	B	207-10	+30°	610.7	610	3120-3480 [1]

Table 1. (continued)

Example no.	X_1	X_2	R_4	R_5	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	found	Retention volume (ml)
30	F	F	CH_3	H	$OC(CH_3)_3$	A+B	170-78	+65°	582.6	582	1290-1920 [5]
31	F	F	CH_3	H	$OC(CH_3)_3$	A	177-79	+100°	582.6	582	255-310 [3]
32	F	F	CH_3	H	$OC(CH_3)_3$	B	190-92	+27°	582.6	582	650-800 [2]
33	F	F	CH_3	H	$OCH_2C(CH_3)_3$	A+B	208-36	+60°	596.7	596	1605-1995 [1]
34	F	F	CH_3	H	$OCH_2C(CH_3)_3$	A	248-56	+98°	596.7	596	1845-2130 [1]
35	F	F	CH_3	H	$OCH_2C(CH_3)_3$	B	226-28	+28°	596.7	596	3270-3750 [1]
36	F	F	CH_3	CH_3	OCH_2CH_3	-	-	-	568.6	568	405-460 [2]

1) On a Sephadex LH-20 column (76x6.3 cm) using chloroform-heptane-ethanol (20:20:1) as mobile phase.

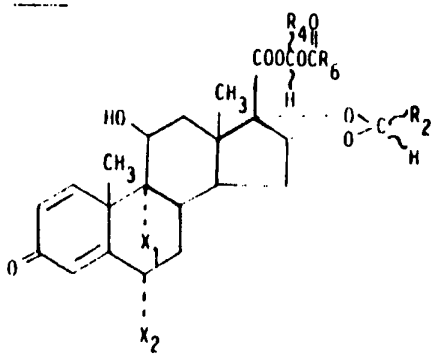
2) On a Sephadex LH-20 column (87.5x2.5 cm) using chloroform-heptane-ethanol (20:20:1) as mobile phase.

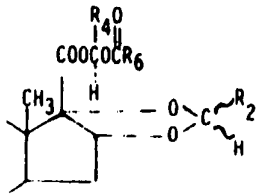
3) On a Sephadex LH-20 column (85x2.5 cm) using chloroform as mobile phase.

4) On a Sephadex LH-20 column (72x6.3 cm) using chloroform as mobile phase.

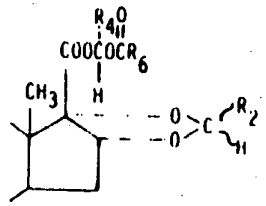
5) On a Sephadex LH-20 column (71.5x6.3 cm) using chloroform as mobile phase.

Table 2.





Epimer A



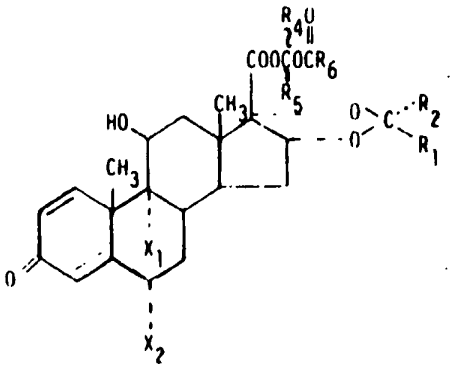
Epimer B

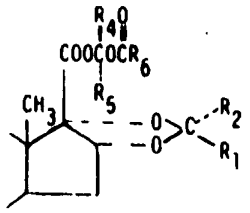
Example no.	X_1	X_2	R_2	R_4	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	Molecular weight found	Retention volume (ml)
37	H	H	CH_3	H	$C(CH_3)_3$	-	189-92	+78°	502.6	502	1290-1665 [1]
38	H	H	$(CH_2)_2CH_3$	H	CH_3	-	63-70	+79°	488.6	488	1110-1260 [1]
39	H	H	$(CH_2)_2CH_3$	H	$C(CH_3)_3$	-	192-96	+74°	530.7	530	1245-1440 [1]
40	F	H	$(CH_2)_2CH_3$	H	$C(CH_3)_3$	-	254-58	+64°	548.7	548	1485-1800 [1]
41	H	H	$(CH_2)_2CH_3$	H	$O(CH_2)_3CH_3$	-	40-46	+70°	546.7	546	1200-1395 [1]
42	H	H	$(CH_2)_2CH_3$	H	$OC(CH_3)_3$	-	155-58	+67°	546.7	546	320-400 [2]
43	H	H	$(CH_2)_2CH_3$	CH_3	OCH_2CH_3	A+B	163-75	+63°	532.6	532	225-285 [2]
44	F	H	$(CH_2)_2CH_3$	CH_3	OCH_2CH_3	A+B	138-60	-	550.6	550	1410-1545 [1]
45	F	F	$(CH_2)_2CH_3$	CH_3	OCH_2CH_3	A+B	160-87	-	568.6	568	1620-2175 [1]

1) On a Sephadex LH-20 column (72x6.3 cm) using chloroform as mobile phase.

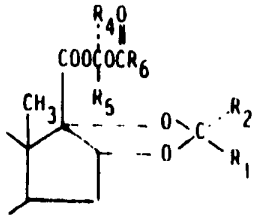
2) On a Sephades LH-20 column (83x2.5 cm) using chloroform as mobile phase.

Table 3.





Epimer A



Epimer B

Example no.	X_1	X_2	R_1	R_2	R_4	R_5	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	Molecular weight found	Retention volume (ml)
46	H	H	CH_3	H	H	H	$C(CH_3)_3$	-	192-97	+67°	12.6	502	1650-1995 [1]
47	H	H	H	CH_3	H	H	$C(CH_3)_3$	-	196-200	+87°	502.6	502	1305-1560 [3]
48	F	H	$(CH_2)_2CH_3$	H	H	H	$C(CH_3)_3$	-	261-67	+69°	548.7	548	1950-2100 [1]
49	F	H	H	$(CH_2)_2CH_3$	H	H	$C(CH_3)_3$	-	255-59	+63°	548.7	548	2145-2370 [1]
50	F	H	$(CH_2)_2CH_3$	H	CH_3	H	CH_3	A	226-31	+101°	520.6	520	1905-2175 [1]
51	F	H	$(CH_2)_2CH_3$	H	CH_3	H	CH_3	B	232-38	+35°	520.6	520	3300-3770 [1]
52	F	H	H	$(CH_2)_2CH_3$	CH_3	H	CH_3	A	176-88	+104°	520.6	520	430-490 [2]
53	F	H	H	$(CH_2)_2CH_3$	CH_3	H	CH_3	B	214-19	+46°	520.6	520	630-715 [2]
54	F	H	H	$(CH_2)_2CH_3$	$CH(CH_3)_2$	H	CH_3	A	133-35	+110°	548.7	548	2100-2400 [1]
55	F	H	H	$(CH_2)_2CH_3$	$CH(CH_3)_2$	H	CH_3	B	210-12	+44°	548.7	548	2850-3225 [1]

Table 3. (continued)

Example no.	X_1	X_2	R_1	R_2	R_4	R_5	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	Molecular weight found	Retention volume (ml)
56	F	H	H	$(CH_2)_2CH_3$	fenyl	H	CH_3	A	235-40	+75°	582.7	582	2100 2400 [1]
57	F	H	H	$(CH_2)_2CH_3$	fenyl	H	CH_3	B	157-82	+75°	582.7	582	2760 3075 [1]
58	H	H	$(CH_2)_2CH_3$	H	H	H	$OC(CH_3)_3$	-	140-42	+77°	546.7	546	1500-1665 [1]
59	H	H	H	$(CH_2)_2CH_3$	H	H	$OC(CH_3)_3$	-	160-65	+69°	546.7	546	1620-1785 [1]
60	F	H	$(CH_2)_2CH_3$	H	H	H	$OC(CH_3)_3$	-	171-73	+66°	564.7	564	250-295 [4]
61	F	H	H	$(CH_2)_2CH_3$	H	H	$OC(CH_3)_3$	-	161-64	+72°	564.7	564	245-290 [4]
62	F	F	H	$(CH_2)_2CH_3$	H	H	OCH_2CH_3	-	203-11	+99°	554.6	554	325-370 [4]
63	F	F	H	$(CH_2)_2CH_3$	H	H	$OCH(CH_3)_2$	-	196-209	+70°	568.6	568	2235-2550 [1]
64	H	H	$(CH_2)_2CH_3$	H	CH_3	H	OCH_2CH_3	A+B	138-52	+102°	532.6	532	300-370 [2]
65	H	H	H	$(CH_2)_2CH_3$	CH_3	H	OCH_2CH_3	A+B	158-91	+33°	532.6	532	400-460 [2]
66	F	H	H	$(CH_2)_2CH_3$	CH_3	H	OCH_2CH_3	A	196-98	+110°	550.7	550	405-475 [2]
67	F	H	H	$(CH_2)_2CH_3$	CH_3	H	OCH_2CH_3	B	212-14	+36	550.7	550	585-670 [2]
68	F	H	$(CH_2)_2CH_3$	H	CH_3	H	$OC(CH_3)_3$	A	154-57	+92°	578.7	578	345-400 [2]
69	F	H	$(CH_2)_2CH_3$	H	CH_3	H	$OC(CH_3)_3$	B	161-68	+27°	578.7	578	485-565 [2]
70	F	H	H	$(CH_2)_2CH_3$	CH_3	H	$OCH(CH_3)_2$	A	221-24	+107°	564.7	564	355-425 [2]
71	F	H	H	$(CH_2)_2CH_3$	CH_3	H	$OCH(CH_3)_2$	B	212-15	+39°	564.7	564	535-635 [2]
72	F	H	H	$(CH_2)_2CH_3$	CH_3	H	$OC(CH_3)_3$	A	168-71	+103°	578.7	578	485-570 [2]
73	F	H	H	$(CH_2)_2CH_3$	CH_3	H	$OC(CH_3)_3$	B	174-79	+31°	578.7	578	255-310 [5]

Table 3. (continued)

Example no.	X_1	X_2	R_1	R_2	R_4	R_5	R_6/YR_6	Epimer	Mp °C	$[\alpha]_D^{25}$ (c=0.2 in CH_2Cl_2)	Molecular weight calc.	Molecular weight found	Retention volume (ml)
74	F	H	$C(CH_3)_3$	H	CH_3	H	OCH_2CH_3	A	220-22	+95°	564.7	564	380-430 [2]
75	F	H	$C(CH_3)_3$	H	CH_3	H	OCH_2CH_3	B	227-37	+18°	564.7	564	540-630 [2]
76	F	H	H	$C(CH_3)_3$	CH_3	H	OCH_2CH_3	A	229-32	+115°	564.7	564	385-455 [2]
77	F	H	H	$C(CH_3)_3$	CH_3	H	OCH_2CH_3	B	246-51	+34°	564.7	564	565-695 [2]
78	F	F	$(CH_2)_2CH_3$	H	CH_3	H	OCH_2CH_3	A	167-70	+95°	568.6	568	300-330 [5]
79	F	F	$(CH_2)_2CH_3$	H	CH_3	H	OCH_2CH_3	B	188-90	+26°	568.6	568	365-395 [5]
80	F	F	H	$(CH_2)_2CH_3$	CH_3	H	OCH_2CH_3	A+B	178-96	+68°	568.6	568	3720-4155 [1]
81	F	F	H	$(CH_2)_2CH_3$	CH_3	H	OCH_2CH_3	A	217-21	+105°	568.6	568	290-340 [5]
82	F	F	H	$(CH_2)_2CH_3$	CH_3	H	OCH_2CH_3	B	211-15	+32°	568.6	568	341-395 [5]
83	F	F	H	$(CH_2)_2CH_3$	CH_3	H	$OCH(CH_3)_2$	A+B	198-210	+67°	582.6	582	2190-3900 [1]
84	F	F	H	$(CH_2)_2CH_3$	CH_3	H	$OCH(CH_3)_2$	A	232-37	+96°	582.6	582	2190-2355 [1]
85	F	F	H	$(CH_2)_2CH_3$	CH_3	H	$OCH(CH_3)_2$	B	225-32	+37°	582.6	582	3630-3900 [1]
86	F	F	H	$(CH_2)_2CH_3$	CH_3	CH_3	OCH_2CH_3	-	-	-	582.6	582	385-440 [2]

1) On a Sephadex LH-20 column (76x6.3 cm) using heptane-chloroform-ethanol (20:20:1) as mobile phase
2) On a Sephadex LH-20 column (87.5x2.5 cm) using heptane-chloroform-ethanol (20:20:1) as mobile phase
3) On a Sephadex LH-20 column (72x6.3 cm) using chloroform as mobile phase
4) On a Sephadex LH-20 column (80x2.5 cm) using chloroform as mobile phase
5) On a Sephadex LH-20 column (81.5 x2.5 cm) using chloroform as mobile phase

Example 87. Pharmaceutical Preparations

The following non-limitative examples illustrate formulations intended for different topical forms of administration. The amount of active steroid in the percutaneous formulations are ordinarily 0.001-0.2%

(w/w), preferably 0.01-0.1% (w/w).

Formulation 1, Ointment

Steroid, micronized	0.025 g
Liquid paraffin	10.0 g
White soft paraffin	ad 100.0 g

Formulation 2, Ointment

Steroid	0.025 g
Propylene glycol	5.0 g
Sorbitan sesquioleate	5.0 g
Liquid paraffin	10.0 g
White soft paraffin	ad 100.0 g

Formulation 3, Oil in water cream

Steroid	0.025 g
Cetanol	5.0 g
Glyceryl monostearate	5.0 g
Liquid paraffin	10.0 g
Cetomacrogol 1000	2.0 g
Citric acid	0.1 g
Sodium citrate	0.2 g
Propylene glycol	35.0 g
Water	ad 100.0 g

Formulation 4, Oil in water cream

Steroid, micronized	0.025 g
White soft paraffin	15.0 g
Liquid paraffin	5.0 g
Cetanol	5.0 g
Sorbimacrogol stearate	2.0 g
Sorbitan monostearate	0.5 g
Sorbic acid	0.2 g
Citric acid	0.1 g
Sodium citrate	0.2 g
Water	ad 100.0 g

Formulation 5, Water in oil cream

Steroid	0.025 g
White soft paraffin	35.0 g
Liquid paraffin	5.0 g
Sorbitan sesquioleate	5.0 g
Sorbic acid	0.2 g
Citric acid	0.1 g
Sodium citrate	0.2 g
Water	ad 100.0 g

Formulation 6, Lotion

Steroid	0.25 mg
Isopropanol	0.5 ml
Carboxyvinylpolymer	3 mg
NaOH	q.s.
Water	ad 1.0 g

Formulation 7, Suspension for injection

Steroid, micronized	0.05-10 mg
Sodium carboxymethylcellulose	7 mg
NaCl	7 mg
Polyoxyethylene (20) sorbitan monoleate	0.5 mg
Phenyl carbinol	8 mg
Water, sterile	ad 1.0 ml

Formulation 8, Aerosol for oral and nasal inhalation

Steroid, micronized	0.1 % w/w
Sorbitan trioleate	0.7 % w/w
Trichlorofluoromethane	24.8 % w/w
Dichlorotetrafluoromethane	24.8 % w/w
Dichlorodifluoromethane	49.6 % w/w

Formulation 9, Solution for atomization

Steroid	7.0 mg
Propylene glycol	5.0 g
Water	ad 10.0 g

Formulation 10, Powder for inhalation

A gelatin capsule is filled with a mixture of

Steroid, micronized	0.1 mg
Lactose	20 mg

The powder is inhaled by means of an inhalation device.

Pharmacology

The affinity of the new androstane-17β-carboxylic acid esters to the glucocorticoid receptor

All steroids according to the present invention are physiologically active compounds. The affinity of the novel androstane-17β-carboxylicacid esters to the glucocorticoid receptor has been used as a model for determination of the anti-inflammatory potency. Their receptor affinities have been compared to budesonide ([22R,S]-16α,17α-butylidenedioxy-11β,21-dihydroxypregna-1,4-diene-3,20-dione) a highly active glucocorticoid with a favourable ratio between local and systemic effects (Thalén and Brattsand, Arzneim.-Forsch. 29, 1687-90 (1979)).

Male Sprague-Dawley rats, one to two months of age, were used throughout the investigation. The thymus was removed and put into ice-cold saline. The tissue was homogenized in a Potter Elvehjem homogenizer in 10 ml of a buffer containing 20 mM Tris, pH 7.4, 10 % (w/v) glycerol, 1 mM EDTA, 20 mM $NaMoO_4$, 10 mM mercaptoethanol. The homogenate was centrifuged for 15 min at 20,000 x g. Portions of the 20,000 x g supernatant (230 μl) were incubated for about 24 h at 0 °C with 100 μl phenylmethylsulphonylfluoride (an esterase inhibitor, final conc. 0.5 mM), 20 μl unlabelled competitor and 50 μl ^{3}H-labelled dexammethasone (final conc. 3 nM). Bound and free steroid were separated by incubating the mixture with 60 μl 2.5 % (w/v) charcoal and 0.25 % (w/v) dextran T70 suspension in 20 mM Tris, pH 7.4, 1 mM EDTA, and 20 mM $MaMoO_4$ for 10 min at 0 °C. Following a centrifugation at 500 x g for 10 min, 230 μl of the supernatant was counted in 10 ml Insta-Gel in a Packard scintillation spectrophotometer. The supernatants were incubated with a) [^{3}H]dexamethasone alone, b) [^{3}H]dexamethasone plus 1000 fold excess of unlabelled dexamethasone and c) [^{3}H]dexamethasone plus 0.03-300 fold "excess" of competitor. The nonspecific binding was determined when 1000 fold excess of unlabelled dexamethasone was added to [^{3}H]-labelled dexammethasone.

The radioactivity bound to the receptor in the presence of competitor divided by the radioactivity bound to the receptor in the absence of competitor multiplied by 100 gives the percentage specific binding of labelled dexamethasone. For each concentration of a competitor the percentage specifically bound radioactivity is plotted against the log of concentration of competitor. The curves are compared at the 50 % specific binding level and referenced to budesonide, which is assigned a relative binding affinity (RBA) of 1.

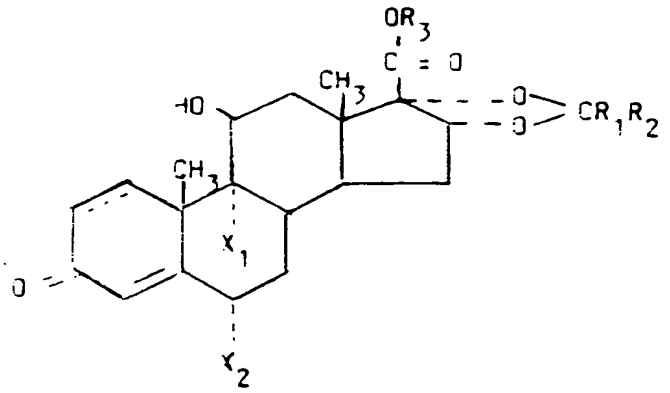
Table 4. Table summarizing relative binding affinities (RBA) to the glucocorticoid receptor of some of the investigated compounds.

Compound according to Ex. No.	RBA
Budesonide	1
2 epimer B	0.30
3 epimer B	0.17
25	0.50
36	0.04
53	0.20
62	0.05
65	0.04
67	0.44
82	1.03
35	0.63

Claims

Claims for the following Contracting States : BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. A compound of the formula



I

or a stereoisomeric compound thereof, in which formula

the 1,2-position is saturated or is a double bond

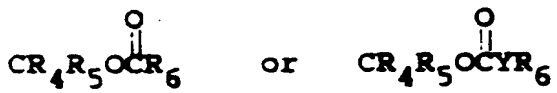
X_1 is selected from hydrogen, fluorine, chlorine and bromine

X_2 is selected from hydrogen, fluorine, chlorine and bromine

R_1 selected from hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon atoms

R_2 is selected from hydrogen or straight and branched hydrocarbon chains having 1-10 carbon atoms and

R_3 is selected from

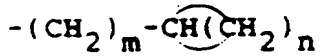


Y is O or S

R_4 is selected from hydrogen, straight or branched hydrocarbon chains having 1-10 carbon atoms or from phenyl

R_5 is selected from hydrogen or methyl and

R_6 is selected from hydrogen, straight or branched, saturated or unsaturated hydrocarbon chains having 1-10 carbon atoms, an alkyl group substituted by at least one halogen atom, a heterocyclic ring system containing 3-10 atoms in the ring system,



(m = 0,1,2; n = 2,3,4,5,6), phenyl or benzyl groups which are unsubstituted or substituted by one or more alkyl, nitro, carboxy, alkoxy, halogen, cyano, carbalkoxy or trifluoromethyl group-(s),

provided that R_1 and R_2 are not simultaneously hydrogen.

2. A compound according to claim 1;

1'-Ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate,

1'-isopropoxycarbonyloxyethyl 9α-fluoro-11B-hydroxy-16α,17α[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate,

1'-propoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]androsta-1,4-diene-3-one-17β-carboxylate,

1'-isopropoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α, 17α[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate,

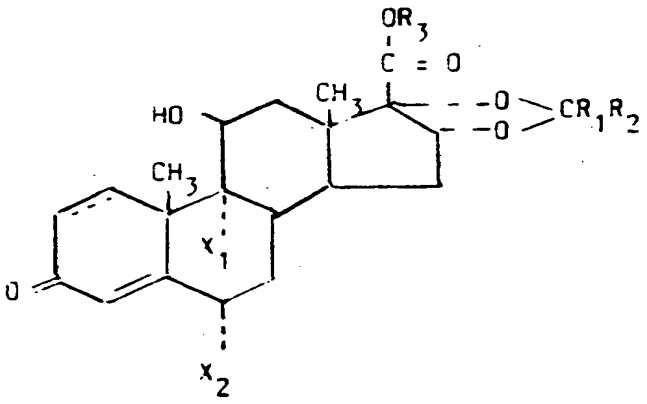
1'-Acetoxyethyl (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate,

1'-Ethoxycarbonyloxyethyl (22R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate,

1'-isopropoxycarbonyloxyethyl (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate,

1'-Ethoxycarbonyloxyethyl (20R)-6α,9α-difluoro-11β-hydroxy-16α-17α-methylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate.

3. A process for the preparation of a compound of the formula



I

or a stereoisomeric component thereof, in which formula

the 1,2-position is saturated or is a double bond

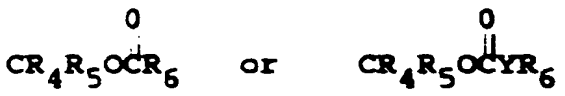
X_1 is selected from hydrogen, fluorine, chlorine and bromine

X_2 is selected from hydrogen, fluorine, chlorine and bromine

R_1 is selected from hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon chains

R_2 is selected from hydrogen or straight or branched hydrocarbon chains having 1-10 carbon atoms and

R_3 is selected from



Y is O or S

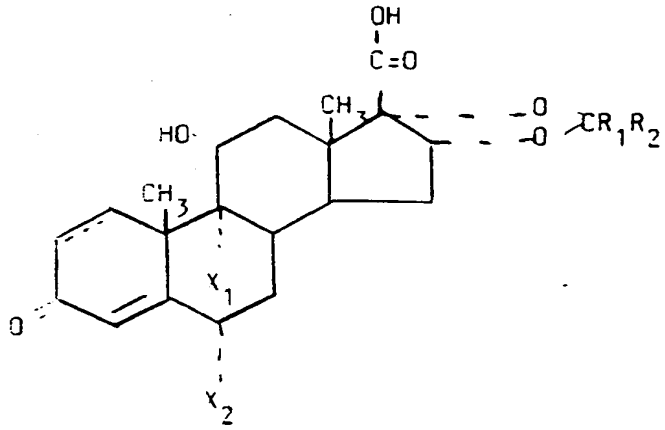
R_4 is selected from hydrogen, straight or branched hydrocarbon chains having 1-10 carbon atoms or from phenyl

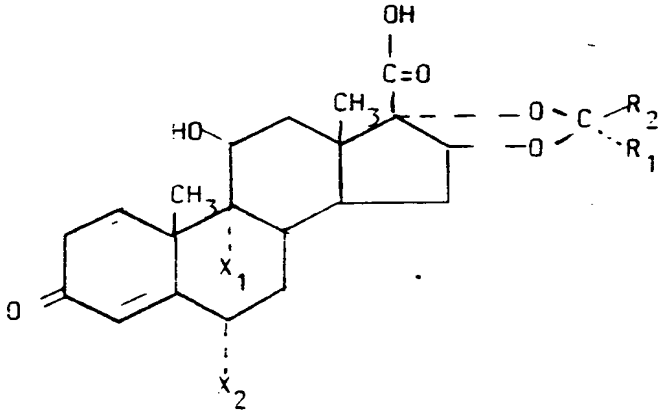
R_5 is selected from hydrogen or methyl and

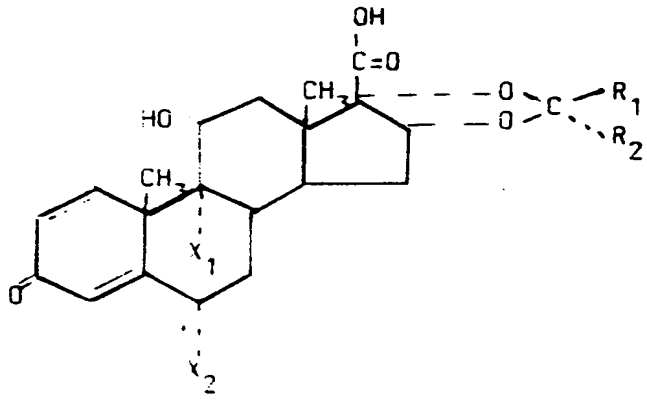
R_6 is selected from hydrogen, straight or branched, saturated or unsaturated hydrocarbon chains having 1-10 carbon atoms, an alkyl group substituted by at least one halogen atom, a heterocyclic ring system containing 3-10 atoms in the ring system,

(m = 0,1,2; n = 2,3,4,5,6), phenyl or benzyl groups which are unsubstituted or substituted by one or more alkyl, nitro, carboxy, alkoxy, halogen, cyano, carbalkoxy or trifluoromethyl group-(s),

provided that R_1 and R_2 are not simultaneously hydrogen, characterized by reaction of a compound of the formula







or a salt thereof with a compound of the formula

in which formulas X_1, X_2, R_1, R_2, Y, R_4, R_5, R_6 and --- have the meaning given above and Z is a halogen atom or a functionally equivalent group, whereafter if the thus obtained ester is an epimeric mixture and a pure epimer is desired, resolving the mixture into stereoisomeric components.

4. A pharmaceutical preparation comprising as active ingredient a compound according to claim 1.

5. A pharmaceutical preparation according to claim 4 in dosage unit form.

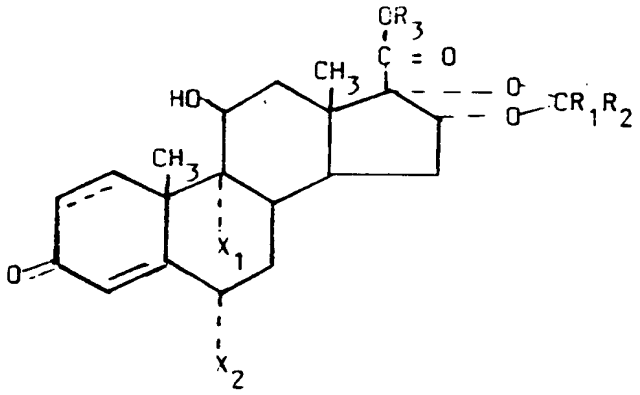
6. A pharmaceutical preparation according to claims 4 and 5 comprising the active ingredient in association with a pharmaceutically acceptable carrier.

7. A compound according to claim 1 for use as an antiinflammatory drug.

8. The use of a compound according to any of the claims 1-2 for preparation of a pharmaceutical preparation comprising as an active ingredient an amount of said compound.

Claims for the following Contracting State : AT

1. A process for the preparation of a compound of the formula



I

or a stereoisomeric compound thereof, in which formula

the 1,2-position is saturated or is a double bond

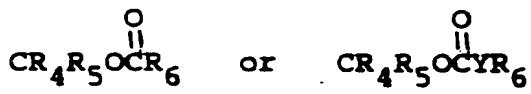
X_1 is selected from hydrogen, flourine, chlorine and bromine

X_2 is selected from hydrogen, flourine, chlorine and bromine

R_1 is selected from hydrogen or a straight or branched hydrocarbon chain having 1-4 carbon chains

R_2 is selected from hydrogen or straight or branched hydrocarbon chains having 1-10 carbon atoms and

R_3 is selected from



Y is O or S

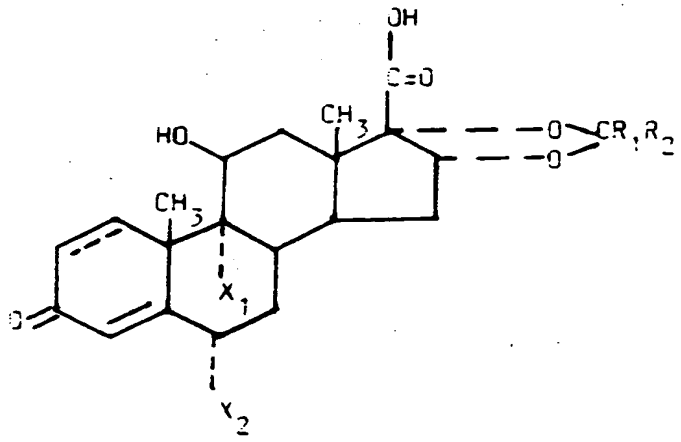
R_4 is selected from hydrogen, straight or branched hydrocarbon chains having 1-10 carbon atoms or from phenyl

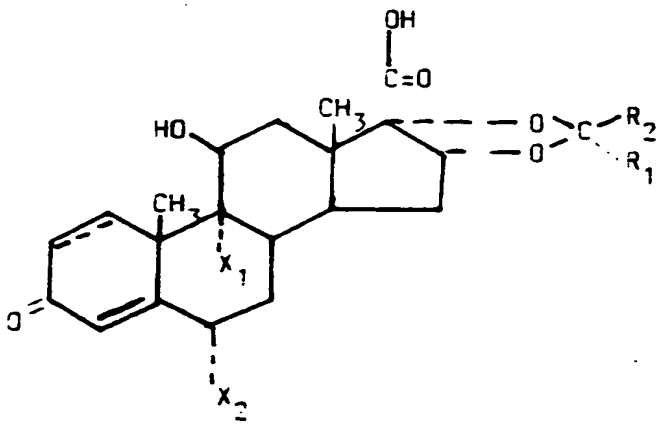
R_5 is selected from hydrogen or methyl and

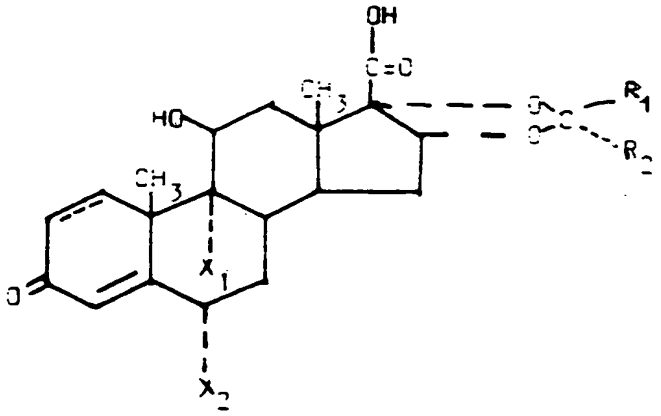
R_6 is selected from hydrogen, straight or branched, saturated or unsaturated hydrocarbon chains having 1-10 carbon atoms, an alkyl group substituted by at least one halogen atom, a heterocyclic ring system containing 3-10 atoms in the ring system, (m = 0,1,2; n = 2,3,4,5,6), phenyl or benzyl groups which are unsubstituted or substituted by one or more alkyl, nitro, carboxy, alkoxy, halogen, cyano, carbalkoxy or trifluoromethyl group(s),

provided that R_1 and R_2 are not simultaneously hydrogen, characterized by reaction of a compound of

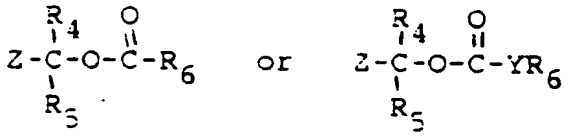
the formula.







or a salt thereof with a compound of the formula



in which formulas X_1, X_2, R_1, R_2, Y, R_4, R_5, R_6 and ⎓ have the meaning given above and Z is a halogen atom or a functionally equivalent group, whereafter if the thus obtained ester is an epimeric mixture and a pure epimer is desired, resolving the mixture into stereoisomeric components.

2. A process according to claim 1, characterized in preparing the compound

1'-Ethoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate,

1'-isopropoxycarbonyloxyethyl 9α-fluoro-11β-hydro-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate,

1'-propoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]androsta-1,4-diene-3-one-17β-carboxylate,

1'-isopropoxycarbonyloxyethyl 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-methylethylidene)bis(oxy)]-androsta-1,4-diene-3-one-17β-carboxylate,

1'-Acetoxyethyl (20R)-9α-fluor-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate,

1'-Ethoxycarbonyloxyethyl (22R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate,

1'-isopropoxycarbonyloxyethyl (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate,

1'-Ethoxycarbonyloxyethyl (20R)-6α,9α-difluoro-11β-hydroxy-16α,17α-propylmethylenedioxyandrosta-1,4-diene-3-one-17β-carboxylate.

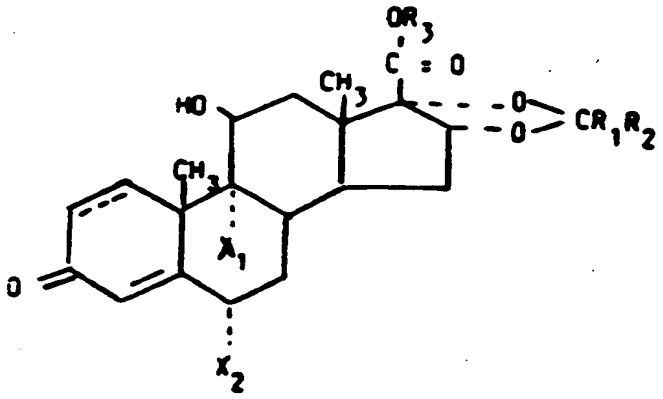
or a stereoisomeric component thereof.

3. The use of a compound according to any of claims 1-2 for the preparation of an anti-inflammatory drug.

Patentansprüche

Patentansprüche für folgende Vertragsstaaten: BE, CH, DE, FR, GB, IT, LI, LU, NL, SE

1. Verbindung der Formel



I

oder eine stereoisomere Verbindung davon, in welcher Formel die Position 1,2 gesättigt ist oder eine doppelte Bindung ist,

X_1 ausgewählt ist aus Wasserstoff, Fluor, Chlor und Brom,

X_2 ausgewählt ist aus Wasserstoff, Fluor, Chlor und Brom,

R_1 ausgewählt ist aus Wasserstoff oder einem gerad- oder verzweigtkettigen Kohlenwasserstoff mit 1 bis 4 Kohlenstoffketten,

R_2 ausgewählt ist aus Wasserstoff oder gerad- oder verzweigtkettigen Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen und

R_3 ausgewählt ist aus

$$CR_4R_5OCR_6 \text{ oder } CR_4R_5OCYR_6 ,$$

Y für O oder S steht,

R_4 ausgewählt ist aus Wasserstoff, gerad- oder verzweigtkettigen Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen oder aus Phenyl,

R_5 ausgewählt ist aus Wasserstoff oder Methyl und

R_6 ausgewählt ist aus Wasserstoff, gerad- oder verzweigtkettigen, gesättigten oder ungesättigten Kohlenwasserstoffen mit 1-10 Kohlenstoffatomen,einer durch zumindest ein Halogenatom substituierten Alkylgruppe, einem heterocyclischen Ringsystem mit 3 bis 10 Atomen im Ringsystem,

$$-(CH_2)_m-CH(CH_2)_n$$

(m = 0,1,2; n = 2,3,4,5, 6), Phenyl- oder Benzylgruppen, welche unsubstituiert oder durch eine oder mehrere Alkyl-, Nitro-, Carboxy-, Alkoxy-, Halogen-, Cyano-, Carbalkoxy- oder Trifluormethylgruppe(n) substituiert sind,

mit der Maßgabe, daß R_1 und R_2 nicht gleichzeitig Wasserstoff sind.

2. Verbindung nach Anspruch 1;

1'-Ethoxycarbonyloxyethyl-6α,9α-difluor-11β-hydroxy-16α,17α-[(1-methylethyliden)-bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Isopropoxycarbonyloxyethyl-9α-fluor-11β-hydroxy-16α,17a-[(1-methylethyliden)- bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Propoxycarbonyloxyethyl-6α,9α-difluor-11β-hydroxy-16α,17α-[(1-methylethyliden)-bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Isopropoxycarbonyloxyethyl-6α,9α-difluor-11β-hydroxy-16α,17α-[(1-methylethyliden)-bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

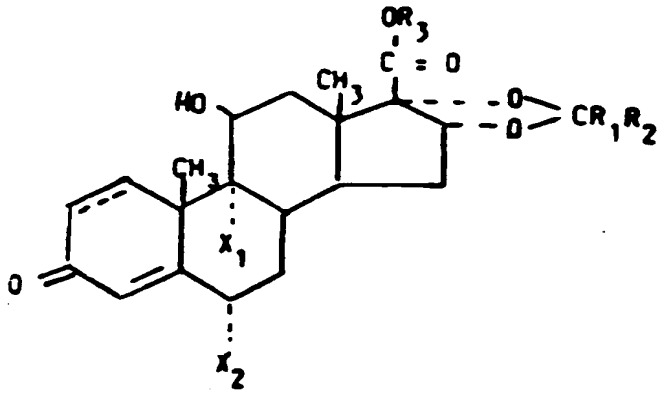
1'-Acetoxyethyl-(20R)-9α-fluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat,

1'-Ethoxycarbonyloxyethyl-(22R)-9a-fluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat,

1'-Isopropoxycarbonyloxyethyl-(20R)-9α-fluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat,

1'-Ethoxycarbonyloxyethyl-(20R)-6α,9α-difluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat.

3. Verfahren zur Herstellung einer Verbindung der Formel



I

oder eines stereoisomeren Bestandteils davon, in welcher Formel
die Position 1,2 gesättigt ist oder eine Doppelbindung ist,

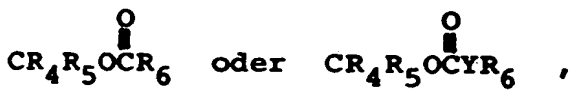
X_1 ausgewählt ist aus Wasserstoff, Fluor, Chlor und Brom,

X_2 ausgewählt ist aus Wasserstoff, Fluor, Chlor und Brom,

R_1 ausgewählt ist aus Wasserstoff oder einem gerad- oder verzweigtkettigen Kohlenwasserstoff mit 1 bis 4 Kohlenstoffketten

R_2 ausgewählt ist aus Wasserstoff oder gerad- oder verzweigtkettigen Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen und

R_3 ausgewählt ist aus



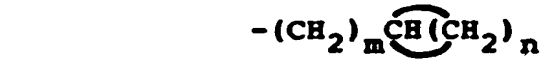
Y für O oder S steht,

R_4 ausgewählt ist aus Wasserstoff, gerad- oder verzweigtkettigen Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen oder aus Phenyl,

R_5 ausgewählt ist aus Wasserstoff oder Methyl und

R_6 ausgewählt ist aus Wasserstoff, gerad- oder verzweigtkettigen, gesättigten oder ungesättigten Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen, einer Alkylgruppe, welche mit zumin-

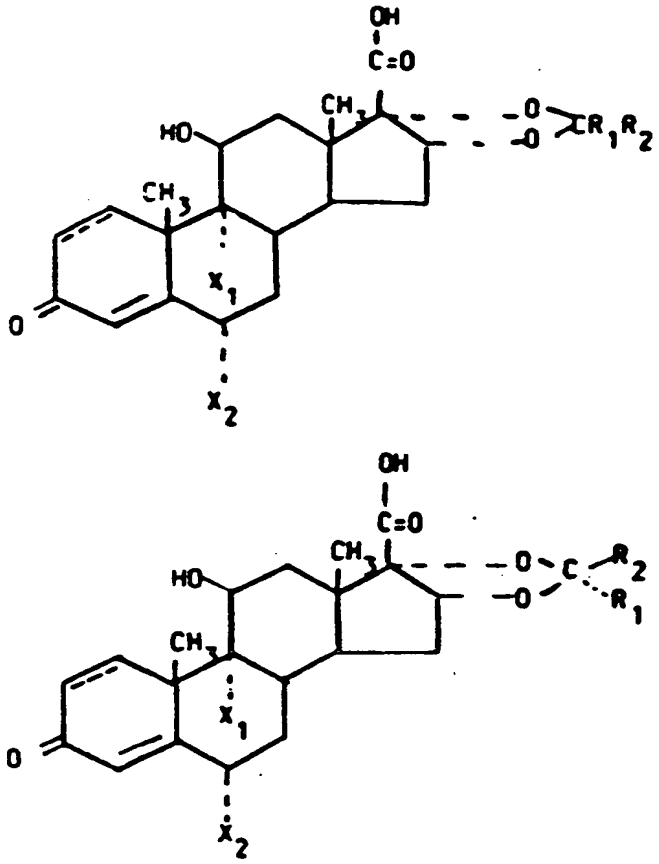
dest einem Halogenatom substituiert ist, einem heterocyclischen Ringsystem, welches 3 bis 10 Atome im Ringsystem umfaßt,

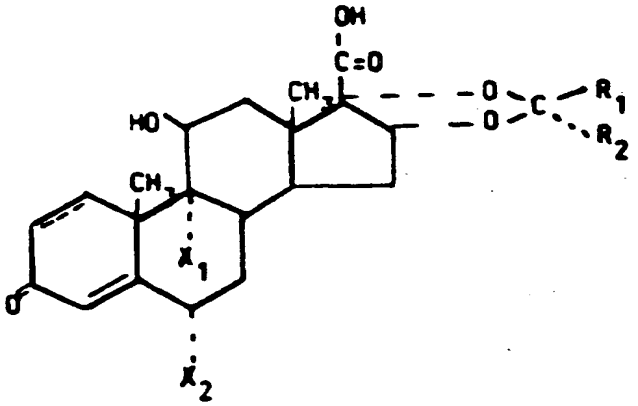


(m = 0,1,2 ; n = 2,3,4,5,6), Phenyl oder Benzylgruppen, welche unsubstituiert sind oder mit einer oder mehreren Alkyl-, Nitro-, Carboxy-, Alkoxy-, Halogen-, Cyano-, Carbalkoxy- oder Trifluormethylgruppe(n) substituiert sind,

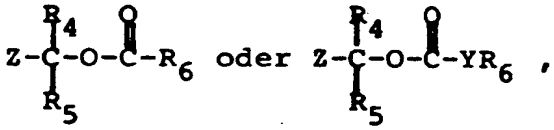
mit der Maßgabe, daß R_1 und R_2 nicht gleichzeitig Wasserstoff sind,

dadurch gekennzeichnet, daß eine Verbindung der Formel





oder ein Salz davon mit einer Verbindung der Formel



in welchen Formeln X_1, X_2, R_1, R_2, Y, R_4, R_5, R_6 und ⎓ die oben angegebene Bedeutung haben, und Z ein Halogenatom oder eine funktionell äquivalente Gruppe ist, umgesetzt wird, wonach, wenn der so erhaltene Ester eine epimere Mischung ist, und ein reines Epimeres gewünscht wird, die Mischung in stereoisomere Bestandteile aufgetrennt wird.

4. Pharmazeutische Präparation, welche als aktives Ingrediens eine Verbindung nach Anspruch 1 umfaßt.

5. Pharmazeutische Zusammensetzung nach Anspruch 4 in Dosiseinheitsform.

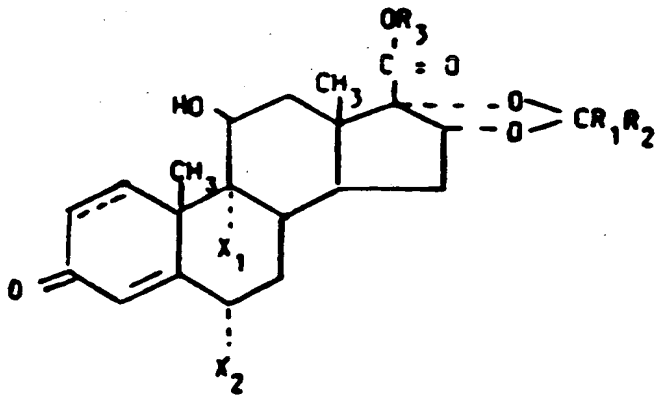
6. Pharmazeutische Präparation nach den Ansprüchen 4 und 5, welche das aktive Ingrediens zusammen mit einem pharmazeutisch akzeptablen Träger umfaßt.

7. Verbindung nach Anspruch 1 zur Verwendung als entzündungshemmendes Arzneimittel.

8. Verbindung nach irgendeinem der Ansprüche 1 bis 2 zur Verwendung für die Herstellung einer pharmazeutischen Präparation, welche als aktives Ingrediens eine Menge dieser Verbindung umfaßt.

Patentansprüche für folgenden Vertragsstaat : AT

1. Verfahren zur Herstellung einer Verbindung der Formel



I

oder einer stereoisomeren Verbindung davon, in welcher Formel
die Position 1,2 gesättigt ist oder eine Doppelbindung ist,

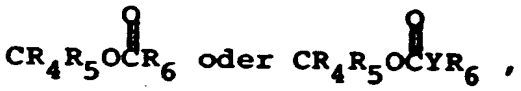
X_1 ausgewählt ist aus Wasserstoff, Fluor, Chlor und Brom,

X_2 ausgewählt ist aus Wasserstoff, Fluor, Chlor und Brom,

R_1 ausgewählt ist aus Wasserstoff oder einem gerad- oder verzweigtkettigen Kohlenwasserstoff mit 1 bis 4 Kohlenstoffketten,

R_2 ausgewählt ist aus Wasserstoff oder gerad- oder verzweigtkettigen Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen und

R_3 ausgewählt ist aus



Y für O oder S steht,

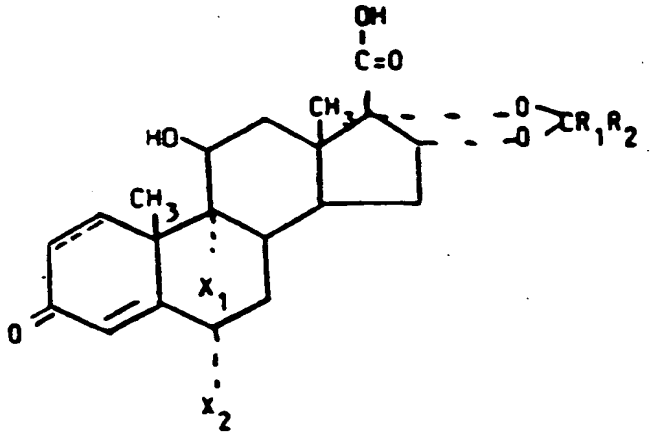
R_4 ausgewählt ist aus Wasserstoff, gerad- oder verzweigtkettigen Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen oder aus Phenyl,

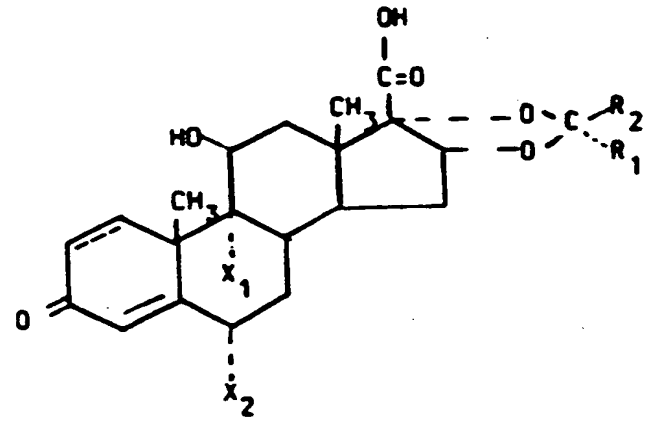
R_5 ausgewählt ist aus Wasserstoff oder Methyl und

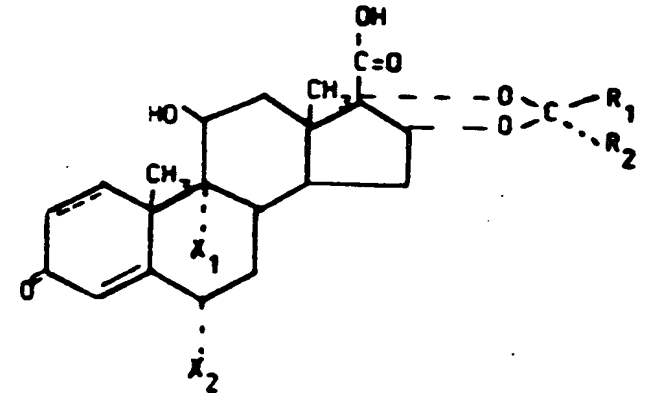
R_6 ausgewählt ist aus Wasserstoff, gerad- oder verzweigtkettigen, gesättigten oder ungesättigten Kohlenwasserstoffen mit 1 bis 10 Kohlenstoffatomen, einer durch zumindest ein Halogenatom substituierten Alkylgruppe, einem heterocyclischen Ringsystem mit 3 bis 10 Atomen im Ringsystem,

(m = 0,1,2; n = 2,3,4, 5,6), Phenyl- oder Benzylgruppen, welche unsubstituiert oder durch eine oder mehrere Alkyl-, Nitro-, Carboxy-, Alkoxy-, Halogen-, Cyano-, Carbalkoxy- oder Trifluormethylgruppe(n) substituiert sind,

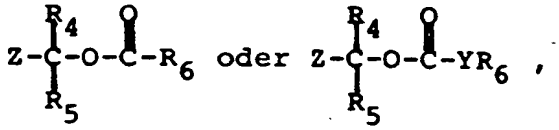
mit der Maßgabe, daß R_1 und R_2 nicht gleichzeitig Wasserstoff sind,
dadurch gekennzeichnet, daß eine Verbindung der Formel







oder ein Salz davon mit einer Verbindung der Formel



in welchen Formeln X_1, X_2, R_1, R_2, Y, R_4, R_5, R_6 und ---die oben angegebene Bedeutung haben, und

Z ein Halogenatom oder eine funktionell äquivalente Gruppe ist, umgesetzt wird, wonach, wenn der so erhaltene Ester eine epimere Mischung ist, und ein reines Epimeres gewünscht wird, die Mischung in stereoisomere Bestandteile aufgetrennt wird.

2. Verfahren nach Anspruch 1, gekennzeichnet durch die Herstellung der Verbindung:

1'-Ethoxycarbonyloxyethyl-6α,9α-difluor-11β-hydroxy-16α,17α-[(1-methylethyliden)- bis(oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Isopropoxycarbonyloxyethyl-9α-fluor-11β-hydro-16α,17α-[(1-methylethyliden)- bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Propoxycarbonyloxyethyl-6α,9α-difluor-11β-hydroxy-16α,17α-[(1-methylethyliden)- bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Isopropoxycarbonyloxyethyl-6α,9α-difluor-11β-hydroxy-16α,17α-[(1-methylethyliden)-bis (oxy)]-androsta-1,4-dien-3-on-17β-carboxylat,

1'-Acetoxyethyl-(20R)-9α-fluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat,

1'-Ethoxycarbonyloxyethyl-(22R)-9α-fluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat,

1'-Isopropoxycarbonyloxyethyl-(20R)-9α-fluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat,

1'-Ethoxycarbonyloxyethyl-(20R)-6α,9α--difluor-11β-hydroxy-16α,17α-propylmethylendioxyandrosta-1,4-dien-3-on-17β-carboxylat

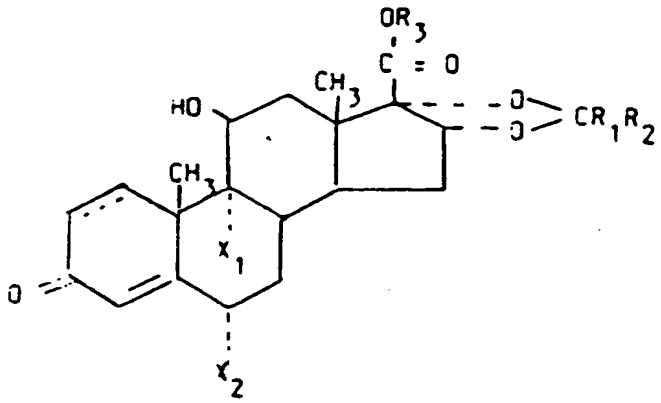
oder eines stereoisomeren Bestandteils davon.

3. Verbindung nach irgendeinem der Ansprüche 1 bis 2 zur Verwendung für die Herstellung eines entzündungshemmenden Arzneimittels.

Revendications

Revendications pour les Etats contractants suivants : BE CH DE FR GB IT LI LU NL SE

1. Composé de formule



I

ou stéréoisomère de celui-ci, dans laquelle formule la position 1,2 est saturée ou est une double liaison,

X_1 est choisi parmi un atome d'hydrogène, de fluor, de chlore ou de brome,

X_2 est choisi parmi un atome d'hydrogène, de fluor, de chlore ou de brome,

R_1 est choisi parmi un atome d'hydrogène et un groupe hydrocarboné à chaîne droite ou ramifiée ayant de 1 à 4 atomes de carbone,

R_2 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, et

R_3 est choisi parmi

$$CR_4R_5OCR_6 \quad \text{et} \quad CR_4R_5OCYR_6$$

Y est O ou S,

R_4 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, et le groupe phényle,

R_5 est choisi parmi un atome d'hydrogène et le groupe méthyle, et

R_6 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés saturés ou non saturés, à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, un groupe alkyle substitué par au moins un atome d'halogène, un système cyclique hétérocyclique contenant de 3 à 10 atomes dans le système cyclique,

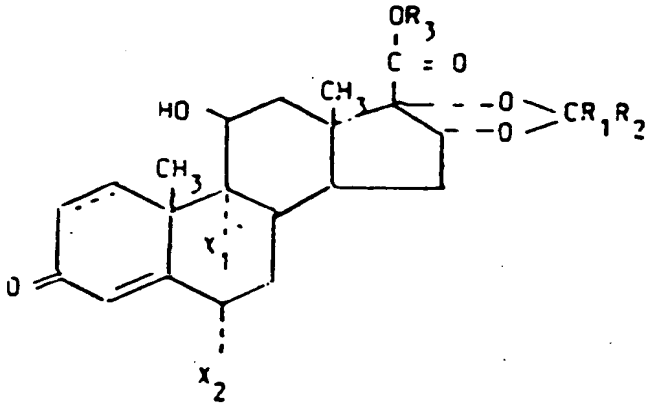
$$-(CH_2)_m-CH(CH_2)_n$$

(m = 0, 1, 2; n = 2, 3, 4, 5, 6), des groupes phényle ou benzyle qui ne sont pas substitués ou qui sont substitués par un ou plusieurs atome(s) d'halogène ou groupe(s) alkyle, nitro, carboxy, alcoxy, cyano, carbalcoxy ou trifluorométhyle,

étant entendu que R_1 et R_2 ne sont pas simultanément des atomes d'hydrogène.

2. Composé selon la revendication 1, qui est:
le 6α,9α-difluoro-11β-hydroxy-16a,17a-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-éthoxycarbonyloxyéthyle,
le 9α-fluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-isopropoxycarbonyloxyéthyle,
le 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-propoxycarbonyloxyéthyle,
le 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-isopropoxycarbonyloxyéthyle,
le (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1-acétoxyéthyle,
le (22R)-9α-fluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1'-éthoxycarbonyloxyéthyle,
le (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1'-isopropoxycarbonyloxyéthyle,
le (20R)-6α,9α-difluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1'-éthoxycarbonyloxyéthyle.

3. Procédé de préparation d'un composé de formule



I

ou d'un stéréoisomère de celui-ci, dans laquelle formule la position 1,2 est saturée ou est une double liaison,

X_1 est choisi parmi un atome d'hydrogène, de fluor, de chlore ou de brome,

X_2 est choisi parmi un atome d'hydrogène, de fluor, de chlore ou de brome,

R_1 est choisi parmi un atome d'hydrogène et un groupe hydrocarboné à chaîne droite ou ramifiée ayant de 1 à 4 atomes de carbone,

R_2 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, et

R_3 est choisi parmi

$$CR_4R_5OCR_6 \quad \text{et} \quad CR_4R_5OCYR_6$$

Y est O ou S,

R_4 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, et le groupe phényle,

R_5 est choisi parmi un atome d'hydrogène et le groupe méthyle, et

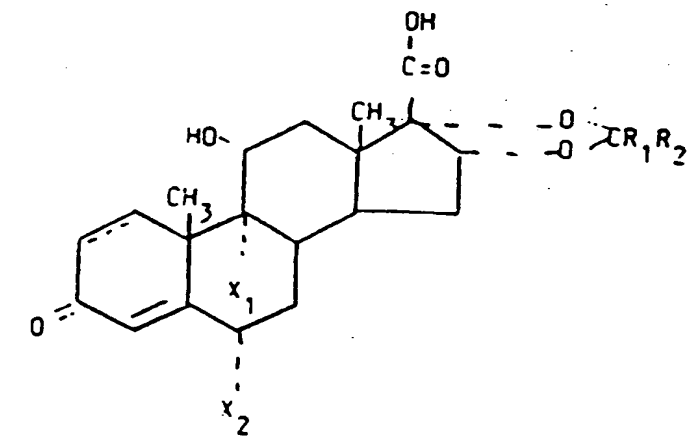
R_6 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés saturés ou non saturés, à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, un groupe alkyle substitué par au moins un atome d'halogène, un système cyclique hétérocyclique contenant de 3 à 10 atomes dans le système cyclique,

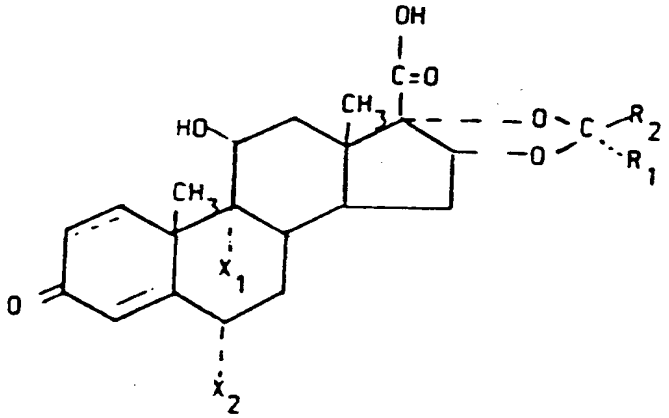
$$-(CH_2)_m-CH(CH_2)_n$$

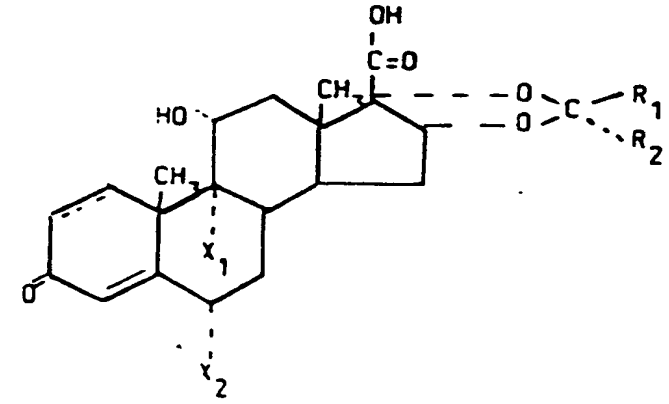
(m = 0, 1, 2; n = 2, 3, 4, 5, 6), des groupes phényle ou benzyle qui ne sont pas substitués ou qui sont substitués par un ou plusieurs atome(s) d'halogène ou groupe(s) alkyle, nitro, carboxy, alcoxy, cyano, carbalcoxy ou trifluorométhyle,

étant entendu que R_1 et R_2 ne sont pas simultanément des atomes d'hydrogène,

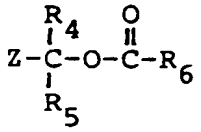
caractérisé par la réaction d'un composé de formule



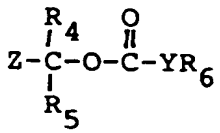




ou d'un sel de celui-ci avec un composé de formule



ou



dans lesquelles formules X_1, X_2, R_1, R_2, Y, R_4, R_5, R_6 et ⎓ ont les mêmes significations que celles

données plus haut et Z est un atome d'halogène ou un groupe fonctionnellement équivalent, et après cela, si l'ester ainsi obtenu est un mélange d'épimères et si l'on désire un épimère pur, la résolution du mélange en composants stéréoisomères.

4. Composition pharmaceutique comprenant, en tant que composant actif, un composé selon la revendication 1.

5. Composition pharmaceutique selon la revendication 4, sous forme de dose unitaire.

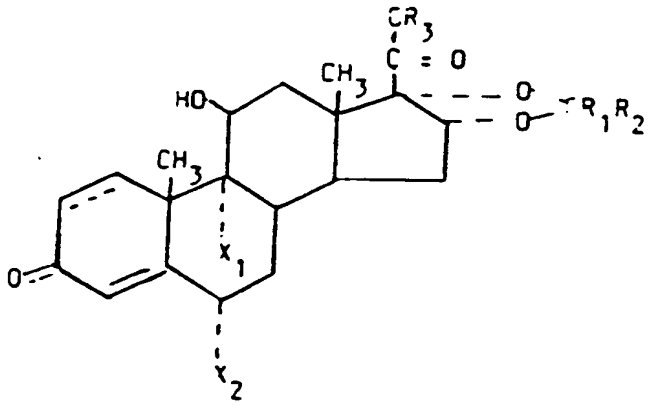
6. Composition pharmaceutique selon les revendications 4 et 5, comprenant le composant actif en association avec un véhicule pharmaceutiquement acceptable.

7. Composé selon la revendication 1, pour utilisation en tant que médicament anti-inflammatoire.

8. Utilisation d'un composé selon la revendication 1 ou 2, pour la préparation d'une composition pharmaceutique comprenant, en tant que composant actif, une quantité dudit composé.

Revendications pour l'Etat contractant suivant : AT

1. Procédé de préparation d'un composé de formule



I

ou d'un stéréoisomère de celui-ci, dans laquelle formule la position 1,2 est saturée ou est une double liaison,

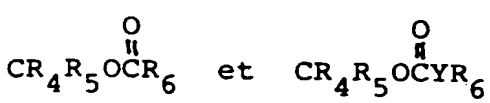
X_1 est choisi parmi un atome d'hydrogène, de fluor, de chlore ou de brome,

X_2 est choisi parmi un atome d'hydrogène, de fluor, de chlore ou de brome,

R_1 est choisi parmi un atome d'hydrogène et un groupe hydrocarboné à chaîne droite ou ramifiée ayant de 1 à 4 atomes de carbone,

R_2 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, et

R_3 est choisi parmi



Y est O ou S,

R_4 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, et le groupe phényle,

R_5 est choisi parmi un atome d'hydrogène et le groupe méthyle, et

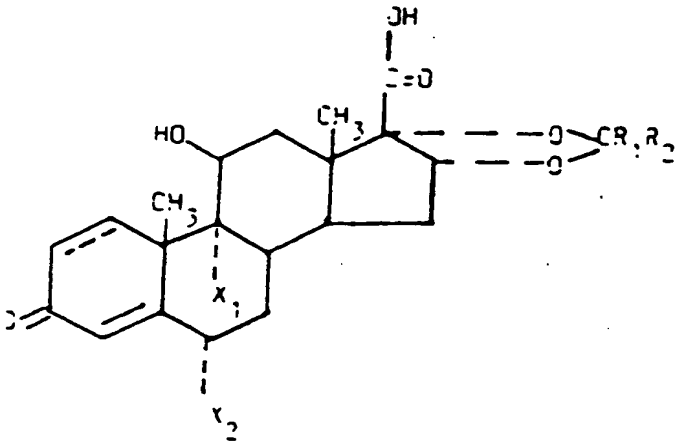
R_6 est choisi parmi un atome d'hydrogène et des groupes hydrocarbonés saturés ou non

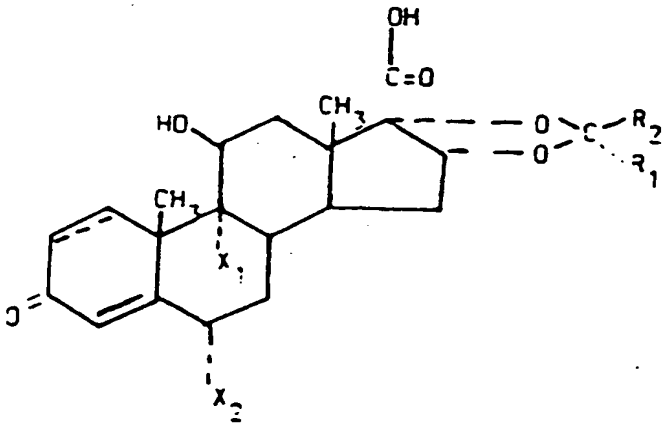
saturés, à chaînes droites ou ramifiées ayant de 1 à 10 atomes de carbone, un groupe alkyle substitué par au moins un atome d'halogène, un système cyclique hétérocyclique contenant de 3 à 10 atomes dans le système cyclique,

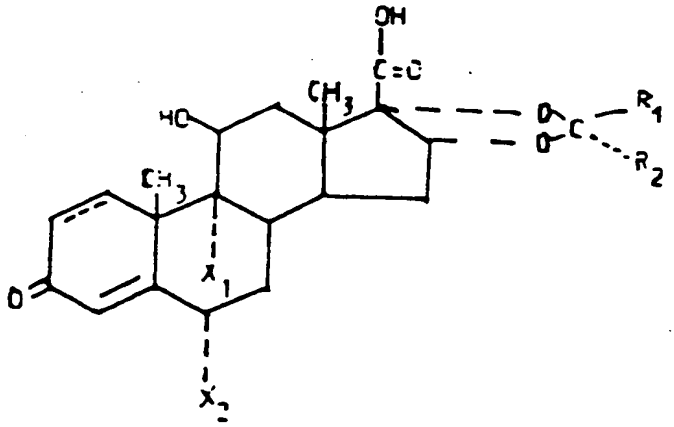
(m = 0, 1, 2; n = 2, 3, 4, 5, 6), des groupes phényle ou benzyle qui ne sont pas substitués ou qui sont substitués par un ou plusieurs atome(s) d'halogène ou groupe(s) alkyle, nitro, carboxy, alcoxy, cyano, carbalcoxy ou trifluorométhyle,

étant entendu que R_1 et R_2 ne sont pas simultanément des atomes d'hydrogène,

caractérisé par la réaction d'un composé de formule







ou d'un sel de celui-ci, avec un composé de formule

dans lesquelles formules X_1, X_2, R_1, R_2, Y, R_4, R_5, R_6 et ⎓ ont les mêmes significations que celles données plus haut et Z est un atome d'halogène ou un groupe fonctionnellement équivalent, et après cela, si l'ester ainsi obtenu est un mélange d'épimères et si l'on désire un épimère pur, la résolution du mélange en composants stéréoisomères.

2. Procédé selon la revendication 1, caractérisé en ce que l'on prépare:
le 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-éthoxycarbonyloxyéthyle,
le 9α-fluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-isopropoxycarbonyloxyéthyle,
le 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-propoxycarbonyloxyéthyle,
le 6α,9α-difluoro-11β-hydroxy-16α,17α-[(1-méthyléthylidène)-bis(oxy)]-androsta-1,4-diène-3-one-17β-carboxylate de 1'-isopropoxycarbonyloxyéthyle,
le (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1-acétoxyéthyle,
le (22R)-9α-fluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1'-éthoxycarbonyloxyéthyle,
le (20R)-9α-fluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1'-isopropoxycarbonyloxyéthyle,
le (20R)-6α,9α-difluoro-11β-hydroxy-16α,17α-propylméthylènedioxyandrosta-1,4-diène-3-one-17β-carboxylate de 1'-éthoxycarbonyloxyéthyle
ou un stéréoisomère de celui-ci.

3. Utilisation d'un composé selon la revendication 1 ou 2, pour la fabrication d'un médicament anti-inflammatoire.